	Hits	Search Text	DBs	Time Stamp
1	0	osteoarthritis near5 mitochondria? with ATP	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:47
2	6	osteoarthritis with ATP	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:48
3	3	chondrocyte? with ATP with synthesis	USPAT; US-PGPUB; EPO; JPO; DERWENT	2004/02/19 14:49

(FILE 'HOME' ENTERED AT 15:04:40 ON 19 FEB 2004)

FILE 'STNGUIDE' ENTERED AT 15:04:47 ON 19 FEB 2004

FILE 'HOME' ENTERED AT 15:04:51 ON 19 FEB 2004

FILE 'CAPLUS, MEDLINE, BIOSIS' ENTERED AT 15:05:05 ON 19 FEB 2004
L1 81 S CHONDROCYTE AND ATP AND SYNTHESIS
L2 39 DUP REMOVE L1 (42 DUPLICATES REMOVED)

FILE 'STNGUIDE' ENTERED AT 15:09:17 ON 19 FEB 2004

L2 ANSWER 21 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 16
ACCESSION NUMBER: 1994:296539 CAPLUS
DOCUMENT NUMBER: 120:296539
TITLE: Nitric oxide and energy production in articular **chondrocytes**
AUTHOR(S): Stefanovic-Racic, M.; Stadler, J.; Georgescu, H. I.; Evans, C. H.
CORPORATE SOURCE: Sch. Medicine, Univ. Pittsburgh, Pittsburgh, PA, 15261, USA
SOURCE: Journal of Cellular Physiology (1994), 159(2), 274-80
CODEN: JCLLAX; ISSN: 0021-9541
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Addition of human, recombinant interleukin-1β (hrIL-1β) to cultures of lapine articular **chondrocytes** provoked a delayed increase in the production of both NO and lactate. These two phenomena followed a similar time course and shared a parallel dose-response sensitivity to hrIL-1β. A causal relation is suggested by the ability of N-monomethyl-L-arginine (NMA), an inhibitor of NO synthase, to blunt the glycolytic response to hrIL-1β. Furthermore, addition of S-nitroso-N-acetylpenicillamine (SNAP), which spontaneously generates NO in culture, increased lactate production to the same degree as IL-1. However, 8-Br-cGMP and isobutylmethylxanthine (IBMX) had no effect, either in the presence or absence of IL-1. Even under standard, aerobic, cell culture conditions, **chondrocytes** consumed little oxygen, either in the presence or absence of IL-1 or NMA. Furthermore, cyanide at concns. up to 100 μM had no effect upon NO **synthesis** or lactate production Thus, the increases in glycolysis under study were not secondary to reduced mitochondrial activity. Although cells treated with IL-1 had increased rates of glycolysis, their concns. of **ATP** fell below those of untreated **chondrocytes** in a time-dependent, but NMA-independent, manner. Transforming growth factor-β (TGF-β) and synovial cytokines (CAF) also increased lactate production However, TGF-β failed to induce NO, and its effect on glycolysis was independent of NMA. Furthermore, cells treated with TGF-β were not depleted in **ATP**. These data are consistent with hypotheses that rates of proteoglycan **synthesis** are, in part, regulated by the intracellular concentration of **ATP** or by changes in pericellular pH. These two possibilities are not mutually exclusive.

L2 ANSWER 12 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 10
ACCESSION NUMBER: 2000:549540 CAPLUS
DOCUMENT NUMBER: 133:279294
TITLE: Mitochondrial oxidative phosphorylation is a downstream regulator of nitric oxide effects on **chondrocyte** matrix **synthesis** and mineralization
AUTHOR(S): Johnson, Kristen; Jung, Alexander; Murphy, Anne; Andreyev, Alexander; Dykens, James; Terkeltaub, Robert
CORPORATE SOURCE: Department of Veterans Affairs Medical Center, University of California, San Diego, CA, USA
SOURCE: Arthritis & Rheumatism (2000), 43(7), 1560-1570
CODEN: ARHEAW; ISSN: 0004-3591
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Increased **chondrocyte** NO and peroxynitrite production appears to modulate decreased matrix **synthesis** and increased mineralization in osteoarthritis (OA). Because NO inhibits mitochondrial respiration, this study was undertaken to directly assess the potential role of **chondrocyte** mitochondrial oxidative phosphorylation (OXPHOS) in matrix **synthesis** and mineralization. The authors studied cultured human articular **chondrocytes** and immortalized costal **chondrocytes** (TC28 cells). The authors also assessed the effects of antimycin A and oligomycin (inhibitors of mitochondrial complexes III and V, resp.) on **chondrocyte** mitochondrial respiration, **ATP synthesis**, and inorg. pyrophosphate (PPi) generation, and the mineralizing potential of released matrix vesicles (MV). Articular **chondrocytes** and TC28 cells respired at comparable rates. Peroxynitrite and NO donors markedly suppressed respiration and **ATP** generation in **chondrocytes**. Because NO exerts multiple effects on **chondrocytes**, the authors investigated the primary functions of mitochondrial respiration and OXPHOS. To do so, the authors identified minimally cytotoxic doses of antimycin and oligomycin, which both induced intracellular **ATP** depletion (by 50-80%), attenuated collagen and proteoglycan **synthesis**, and blocked transforming growth factor β from increasing intracellular **ATP** and elaboration of PPi, a critical inhibitor of hydroxyapatite deposition. Antimycin and oligomycin also abrogated the ability of the **ATP**-hydrolyzing enzyme plasma cell membrane glycoprotein 1 (PC-1) to increase **chondrocyte** PPi generation. Finally, MV from cells treated with antimycin or oligomycin contained less PPi and precipitated >50% more 45Ca. **Chondrocyte** mitochondrial reserve, as NO-sensitive mitochondrial respiration-mediated **ATP** production, appears to support matrix **synthesis** and PPi elaboration and to regulate MV composition and mineralizing activity. NO-induced depression of **chondrocyte** respiration could modulate matrix loss and secondary cartilage mineralization in OA.
REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 29 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 21
ACCESSION NUMBER: 1989:567362 CAPLUS
DOCUMENT NUMBER: 111:167362
TITLE: Metabolic effects of forskolin in chick **chondrocytes**
AUTHOR(S): Hu, Lie Min; Kemp, Stephen F.; Elders, M. Joycelyn; Smith, W. Grady
CORPORATE SOURCE: Dep. Biochem., Univ. Arkansas, Little Rock, AR, 72205, USA
SOURCE: Biochimica et Biophysica Acta (1989), 1013(3), 294-9
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of forskolin on parameters of energy metabolism and proteoglycan **synthesis** were investigated in chick embryo sternal **chondrocyte** cultures. After 8 h exposure to 100 μM forskolin, **ATP** levels and O consumption were unaltered. Protein **synthesis** was unaffected by ≤ 50 μM forskolin and protein degradation was unaffected by forskolin ≤ 100 μM. In contrast, incorporation of the proteoglycan precursors, 35SO4 and [3H]glucosamine, was more sensitive to forskolin. Inhibition was linear at 10-100 μM, reaching 70% at 100 μM. Incorporation of 35SO4 into glycosaminoglycan chains initiated on an artificial β-xyloside acceptor was inhibited in the same manner. CAMP accumulation was maximal at 10 μM forskolin, a concentration which did not alter proteoglycan **synthesis**. A major, acute effect of forskolin in these short-term expts. is inhibition of proteoglycan **synthesis** in a cAMP-independent manner.

L2 ANSWER 3 OF 39 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003165159 MEDLINE
DOCUMENT NUMBER: 22569537 PubMed ID: 12682616
TITLE: The role of free radicals in the pathogenesis of rheumatoid arthritis.
AUTHOR: Hadjigogos K
CORPORATE SOURCE: Central Hospital, Thessaloniki, Greece.
SOURCE: PANMINERVA MEDICA, (2003 Mar) 45 (1) 7-13. Ref: 66
Journal code: 0421110. ISSN: 0031-0808.
PUB. COUNTRY: Italy
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030409
Last Updated on STN: 20030730
Entered Medline: 20030729

AB Free radicals are reactive chemical species that differ from other compounds in that they have unpaired electrons in their outer orbitals. They are capable of damaging cellular components, and accumulating evidence suggests that they may contribute to various disease entities including inflammatory joint disease. Reactive oxygen species (ROS) as well as reactive nitrogen species (RNS) can directly or indirectly damage basic articular constituents and lead to the clinical expression of the inflammatory arthritis. Hydroxyl radicals degrade isolated proteoglycans, and HOCl fragments collagen. Hydrogen peroxide, which is very diffusible, readily inhibits cartilage proteoglycan **synthesis**, e.g. by interfering with **ATP synthesis**, in part by inhibiting the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase in **chondrocytes**, aggravating the effects of proteolytic and free-radical-mediated cartilage degradation. Peroxynitrite and HOCl may facilitate cartilage damages by inactivating TIMPs. TIMP-1 inhibits stromelysins, collagenases and gelatinases and this ability is lost after ONOO(-) or HOCl treatment. HOCl can also activate latent forms of neutrophil collagenases and gelatinase with obvious consequences. Hypochlorous acid, ONOO(-) and O(2)(*-) react with ascorbate, which is essential for cartilage function, leading to low levels of ascorbate in synovial fluid. Low concentrations of H2O(2), O(2)(*-) or both, accelerate bone resorption by osteoclasts, whereas NO. inhibits it. NO. promotes **chondrocyte** apoptosis, inhibits proteoglycan **synthesis** and activates latent metalloproteinases and cyclooxygenase. ROS, produced by activated phagocytes, could alter the antigenic behaviour of immunoglobulin G, producing fluorescent protein aggregates that can further activate phagocytic cells. Radical-exposed IgG is able to bind rheumatoid factor and results in the generation of C3alpha. This reaction may be self-perpetuating within the rheumatoid joint, suggesting that free radicals play a role in the chronicity of the inflammatory reaction which is a key question regarding to which extent free radicals contribute to the consequences of inflammation, such as the cartilage and bone destruction. Reactive oxygen intermediates can also function as signaling messengers to activate transcription factors, like NFkB and AP-1, and induce gene expression. All this knowledge might serve to apply a rational selection of antioxidants for possible therapeutic purposes, enforcing combination therapy of the inflammatory joint disease.

L2 ANSWER 6 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2002:199564 CAPLUS

DOCUMENT NUMBER: 136:338401

TITLE: The mitochondrion in osteoarthritis

AUTHOR(S): Terkeltaub, Robert; Johnson, Kristen; Murphy, Anne; Ghosh, Soumitra

CORPORATE SOURCE: Veterans Affairs San Diego Health Care System, University of California, San Diego, CA, 92161, USA

SOURCE: Mitochondrion (2002), 1(4), 301-319
CODEN: MITOCN; ISSN: 1567-7249

PUBLISHER: Elsevier Science B.V.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. In a variety of tissues, cumulative oxidative stress, disrupted mitochondrial respiration, and mitochondrial damage promote aging, cell death, and ultimately, functional failure and degeneration. Because articular cartilage of **chondrocytes** are highly glycolytic, mitochondria- mediated pathogenesis has not been previously applied in models for pathogenesis of osteoarthritis (OA), a cartilage degenerative disease that increases markedly in aging. However, **chondrocyte** mitochondria respire in vitro and they demonstrate swelling and changes in number in situ in the course of OA. Normal **chondrocyte** mitochondrial function is hypothesized to critically support **ATP** (**ATP**) reserves in functional stressed **chondrocytes** during OA evolution. In this model, disruption of **chondrocyte** respiration by nitric oxide, a mediator markedly up-regulated in OA cartilage, is centrally involved in **chondrocyte** functional compromise. Furthermore, mitochondrial dysfunction can mediate several specific pathogenic pathways implicated in OA. These include oxidative stress, inadequacy of **chondrocyte** biosynthetic and growth responses, up-regulated **chondrocyte** cytokine-induced inflammation and matrix catabolism, increased **chondrocyte** apoptosis, and pathol. cartilage matrix calcification. In addition, the direct, sublethal impairment of **chondrocyte** mitochondrial **ATP synthesis** in vitro decreases matrix **synthesis** and increases matrix calcification ("disease in a dish"). The weight of evidence reviewed herein strongly supports **chondrocyte** mitochondrial impairment as a mediator of the establishment and progression of OA.

REFERENCE COUNT: 166 THERE ARE 166 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT